

**DEVELOPMENT OF FUNCTIONALLY GRADED BIOMATERIAL WITH
TAILORABLE DEGRADATION RATE AND MECHANICAL
PROPERTIES**

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by

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Submitted

in fulfilment of the requirements of the degree of Doctor of Philosophy

to the



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DEDICATED TO
ALMIGHTY AND MY PARENTS

Certificate

This is to certify that the thesis entitled '**Development of Functionally Graded Biomaterial with Tailorable Degradation Rate and Mechanical Properties**' submitted by **Mr. Gaurav Tripathi** to the Indian Institute of Technology Delhi, for the award of the degree of ***Doctor of Philosophy*** is a record of the original bonafide research work carried out by him under my guidance and supervision. The results contained in it have not been submitted in part or full to any other institute or university for the award of any degree/diploma.



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(Gaurav Tripathi)

Abstract

Biomaterials are frequently employed in modern medicine to treat and replace damaged or degenerating tissues and organs. Biodegradable metal implants are gaining attention over traditional bio-inert/bio-stable implants owing to the fact that most of the clinical problems need only short-term support while healing. These implants degrade by releasing metallic components that the body metabolizes and are finally replaced by bone tissue. Metals like iron (Fe), zinc (Zn) and magnesium (Mg) are gaining the attention of researchers in the field of biomedical implants owing to their good mechanical and biodegradable properties. However, there are various problems associated with each of these materials like very fast or very slow degradation rate, stress shielding, poor mechanical properties etc. Rapid corrosion of Mg in the physiological surroundings due to hydrogen release leads to corrosion and mechanical integrity issues. Fe has good mechanical properties, but its high elastic modulus and slow rate of degradation limit its use in the biomedical field. Zn has ideal degradation rate but its inferior mechanical properties inhibit the application of zinc as biomaterial.

Also, bioceramics like hydroxyapatite (HAp) can be added in low concentrations to facilitate bone ingrowth and ensure an effective bond between bone and implant material. The implant surface must possess bioactive properties that encourage the growth of bone cells and the formation of biological apatite, hence enhancing osteoconductivity. All these problems could be resolved by fabricating composite and functional biomaterials, combining the advantages of two or more materials into a single biomaterial. Moreover, tailorable degradation rate and mechanical properties could be achieved by fabrication of a topologically ordered functionally graded composite (TOFGC) biomaterial. The literature survey indicates about the limited reported work in the direction of fabrication and

characterization Fe and Zn based TOFGC biomaterial by making use of additive manufacturing and pressureless microwave sintering.

To address this research gap, a novel methodology has been developed for the fabrication of Fe-Hap-Zn TOFGC biomaterial utilizing the additive manufacturing, pressureless microwave sintering, and casting processes. Carbonyl iron particles (CIPs), HAp powder and high purity Zn ingots were used in sample fabrication. The mould preparation for the fabrication of Fe-HAp was done with the help of a phosphate-based investment material. Response surface methodology (RSM) was used for planning of experimentation to determine the effect of sintering temperature, soaking time, HAp percentage and heating rate on responses namely shrinkage, sintered density and compressive yield strength (CYS). Genetic Algorithm (GA) based multi-objective optimization was performed to obtain the optimum process parameters. The optimized parameters were found as: sintering temperature = 836 °C, soaking time = 45 min, HAp (wt %) = 3.5% and heating rate = 13 °C/min, which resulted in 6.92% shrinkage, 5.98 g/cm³ sintered density and 164.88 MPa of CYS. The Scanning electron microscopy (SEM) of the fabricated Fe-HAp samples demonstrated successful bonding of CIPs without the need of any compaction pressure. X-ray diffraction (XRD) plots and energy dispersive spectroscopy (EDS) analysis confirmed the presence of HAp embedded in the Fe matrix without any contamination from the mould material.

It can be inferred from the literature that TOFGC biomaterials have the potential to overcome the problems faced by conventional biomaterials. Hence for the case study four Fe-HAp-Zn TOFGC biomaterials with different types of Zn infiltrations were fabricated using the developed methodology. The apparent density, porosity, CYS and modulus of elasticity were found to be varying in a wide range of 1.95-5.36 g/cm³, 28.37-73.99 %, 17.62-102.32 MPa and 186.12-2452.20 MPa respectively. Moreover, the degradation

behaviour of samples was examined in simulated body fluid (SBF) solution at 37 °C and corrosion rate of four samples was found to vary in range of 1.68-4.33 *mm*²*py*. These properties were found comparable to that of bone and can be altered to mimic the cancellous as well as cortical bone.

Furthermore, in the present work, studies were performed for degradation behaviour, *in vitro* cytocompatibility and hemocompatibility of the fabricated TOFGC samples. The degradation behaviour of the samples was analyzed using immersion tests in SBF, and potentiodynamic polarization (PP) and electrochemical impedance spectroscopy (EIS) measurements. On the basis of immersion test and electrochemical tests, it was deduced that rate of degradation increased on inclusion of HAp in the pure Fe matrix, which was attributed to formation of micro galvanic cell in the Fe-HAp biomaterial. The infiltration of Zn into the Fe-HAp matrix led to a substantial increase in the rate of degradation. The reason was attributed to the formation of a galvanic cell, in which Fe-HAp acted as the cathode and Zn acted as the anode. With an increase in Zn wt.%, the corrosion potential was found to shift towards more negative side and corrosion current density was found to increase, thereby indicating reduced corrosion resistance. The pure Fe dense sample showed minimum weight loss and corrosion rate, whereas Fe-3.5HAp-54Zn depicted maximum weight loss and corrosion rate in immersion and electrochemical testing respectively. The maximum weight loss and corrosion rate for Fe-3.5HAp-54Zn was found to be 6.98 % and 2.38 *mm*²*py* respectively. All samples were found to have good cytocompatibility. Fe-HAp-Zn biomaterial showed maximum cell viability, which was attributed to the fact that Zn is more biocompatible than Fe. All samples showed hemolysis ratio within the prescribed limit (less than 5%). Furthermore, Fe-HAp-Zn showed minimum platelet adhesion, depicted excellent antithrombotic property.

Dimensional analysis utilizing Buckingham's π theorem was performed to derive the models for prediction of weight loss in immersion test and corrosion rate in electrochemical test. The values predicted by the proposed models exhibited a strong concurrence with the experimental results. The maximum error in prediction of weight loss and corrosion was found to be 5.81% and 3.91% respectively. In the comparative study TOFGC Fe-HAp-Zn biomaterial demonstrated enhanced degradation characteristics as well as excellent cytocompatibility and hemocompatibility in comparison to current metallic biodegradable materials. It was established that the developed Fe-HAp-Zn biomaterial has the potential to be a biodegradable material for orthopaedic applications because of its improved corrosion rate, reduced hemolysis ratio, and outstanding antithrombotic property. Also, the mechanical and degradation properties of the developed biomaterial could be tailored to match the suitable application.

सार

क्षतिग्रस्त या खराब हो रहे ऊतकों और अंगों के उपचार और प्रतिस्थापन के लिए आधुनिक चिकित्सा में अक्सर बायोमटेरियल का उपयोग किया जाता है। बायोडिग्रेडेबल धातु प्रत्यारोपण इस तथ्य के कारण पारंपरिक जैव-अक्रिय/जैव-स्थिर प्रत्यारोपण पर ध्यान आकर्षित कर रहे हैं कि अधिकांश नैदानिक समस्याओं को ठीक करते समय केवल अल्पकालिक सहारे की आवश्यकता होती है। ये प्रत्यारोपण धातु घटकों का विमोचन करके विघटित हो जाते हैं जिन्हें शरीर चयापचय करता है और अंततः हड्डी के ऊतकों द्वारा प्रतिस्थापित किया जाता है। आयरन (Fe), जिंक (Zn) और मैगनीशियम (Mg) जैसी धातुएँ अपने अच्छे यांत्रिक और बायोडिग्रेडेबल गुणों के कारण बायोमेडिकल प्रत्यारोपण के क्षेत्र में शोधकर्ताओं का ध्यान आकर्षित कर रही हैं। हालाँकि, इनमें से प्रत्येक सामग्री से जुड़ी विभिन्न समस्याएँ हैं जैसे बहुत तेज या बहुत धीमी विघटन दर, तनाव परिरक्षण, खराब यांत्रिक गुण आदि। हाइड्रोजन रिलीज के कारण शारीरिक परिवेश में Mg का तेजी से क्षरण संक्षारण और यांत्रिक समग्रता के मुद्दों को जन्म देता है। Fe में अच्छे यांत्रिक गुण हैं, लेकिन इसका उच्च लोचदार मापांक और विघटन की धीमी दर जैव चिकित्सा क्षेत्र में इसके उपयोग को सीमित करती है। Zn में आदर्श क्षरण दर होती है लेकिन इसके निम्न यांत्रिक गुण बायोमटेरियल के रूप में जिंक के प्रयोग को रोकते हैं।

इसके अलावा, हड्डियों के विकास को सुविधाजनक बनाने और हड्डी और प्रत्यारोपण सामग्री के बीच एक प्रभावी बंधन सुनिश्चित करने के लिए हाइड्रॉक्सीपैटाइट (HAp) जैसे बायोसेरामिक्स को कम मात्रा में मिलाया जा सकता है। इम्प्लांट की सतह में बायोएक्टिव गुण होने चाहिए जो हड्डी की कोशिकाओं के विकास और जैविक एपेटाइट के निर्माण को प्रोत्साहित करते हैं, जिससे ऑस्टियोकंडक्टिविटी बढ़ती है। इन सभी समस्याओं को मिश्रित और कार्यात्मक बायोमटेरियल बनाकर, दो या दो से अधिक सामग्रियों के फायदों को एक ही बायोमटेरियल में मिलाकर हल किया जा सकता है। इसके अलावा, टोपोलॉजिकल ऑर्डर्ड और कार्यात्मक रूप से वर्गीकृत कम्पोजिट (TOFGC) बायोमटेरियल के

निर्माण द्वारा अनुरूप क्षरण दर और यांत्रिक गुणों को प्राप्त किया जा सकता है। साहित्य सर्वेक्षण एडिटिव मैनुफैक्चरिंग और प्रेशरलेस माइक्रोवेव सिंटरिंग का उपयोग करके Fe और Zn आधारित TOFGC बायोमटेरियल के निर्माण और चरित्रांकन की दिशा में सीमित रिपोर्ट किए गए कार्य के बारे में इंगित करता है।

इस शोध अंतर को संबोधित करने के लिए, एडिटिव मैनुफैक्चरिंग, प्रेशरलेस माइक्रोवेव सिंटरिंग और कास्टिंग प्रक्रियाओं का उपयोग करके Fe-HAp-Zn TOFGC बायोमटेरियल के निर्माण के लिए एक नई पद्धति विकसित की गई है। नमूना निर्माण में कार्बोनिल आयरन पाउडर (CIP), HAp पाउडर और उच्च शुद्धता वाले Zn सिल्लियों का उपयोग किया गया था। Fe-HAp कम्पोजिट के निर्माण के लिए मोल्ड का निर्माण फॉस्फेट-आधारित इन्वेस्टमेंट पाउडर की मदद से किया गया था। रिस्पांस सरफेस मेथडोलॉजी (RSM) का उपयोग सिंटरिंग तापमान, सोकिंग टाइम, HAp प्रतिशत और हीटिंग दर के प्रभाव को रेस्पॉन्सेस अर्थात् संकुचन, सिंटर घनत्व और कम्प्रेसिव यील्ड स्ट्रेंथ (CYS) पर निर्धारित करने के लिए प्रयोग की योजना के लिए किया गया। ऑप्टिमाइज़्ड प्रक्रिया पैरामीटर प्राप्त करने के लिए जेनेटिक एल्गोरिदम (GA) आधारित मल्टी ऑब्जेक्टिव ऑप्टिमाइजेशन का प्रयोग किया गया था। ऑप्टिमाइज़्ड पैरामीटर इस प्रकार पाए गए: सिंटरिंग तापमान = 836 °C, सोकिंग टाइम = 45 मिनट, HAP (wt %) = 3.5% और हीटिंग दर = 13 °C/मिनट, जिसके परिणामस्वरूप 6.92% संकुचन, 5.98 g/cm³ सिंटर घनत्व और 164.88 MPa CYS की वैल्यू पाई गई। निर्मित Fe-HAp नमूनों की स्कैनिंग इलेक्ट्रॉन माइक्रोस्कोपी (SEM) ने किसी भी संघनन दबाव की आवश्यकता के बिना CIP की सफल बॉन्डिंग प्रदर्शित की। एक्स-रे डिफ्रैक्शन (XRD) प्लॉट और एनर्जी डिसपर्सिव स्पेक्ट्रोस्कोपी (EDS) विश्लेषण ने मोल्ड सामग्री से किसी भी संदूषण के बिना Fe मैट्रिक्स में एम्बेडेड HAp की उपस्थिति की पुष्टि की।

साहित्य से यह अनुमान लगाया जा सकता है कि TOGGC बायोमटेरियल्स में पारंपरिक बायोमटेरियल्स के सामने आने वाली समस्याओं को दूर करने की क्षमता है। इसलिए केस स्टडी के लिए विकसित पद्धति का उपयोग करके विभिन्न प्रकार के Zn इंफिल्ट्रेशन के साथ चार Fe-HAp-Zn TOFGC बायोमटेरियल का निर्माण किया गया। घनत्व, पोरसिटी, CYS और लोच का मापांक क्रमशः 1.95-5.36 g/cm³, 28.37-73.99%, 17.62-102.32 MPa और 186.12-2452.20 MPa की विस्तृत रेंज में पाया गया। इसके अलावा, नमूनों के क्षरण व्यवहार की जांच सिम्युलेटेड बॉडी फ्लूइड (SBF) सोल्यूशन में 37 °C पर की गई और चार नमूनों की संक्षारण दर 1.68-4.33 mmpy की सीमा में पाई गई। ये गुण हड्डी के तुलनीय पाए गए और इन्हें कैंसलस और कॉर्टिकल हड्डी की नकल करने के लिए बदला जा सकता है।

इसके अलावा, वर्तमान कार्य में, निर्मित TOFGC नमूने इन विट्रो साइटोकोम्पैटिबिलिटी, हेमोकोम्पैटिबिलिटी और क्षरण व्यवहार के लिए अध्ययन किए गए। नमूनों के क्षरण व्यवहार का विश्लेषण SBF में इमर्शन परीक्षण, पोटेन्शियोडायनामिक पोलराइज़ेशन (PP) और इलेक्ट्रोकेमिकल इम्पीडेन्स स्पेक्ट्रोस्कोपी (EIS) का उपयोग करके किया गया। इमर्शन परीक्षण और इलेक्ट्रोकेमिकल परीक्षणों के आधार पर, यह निष्कर्ष निकाला गया कि शुद्ध Fe मैट्रिक्स में HAp को शामिल करने पर क्षरण की दर में वृद्धि हुई, जिसके लिए Fe-HAp बायोमटेरियल में माइक्रो गैल्वेनिक सेल के गठन को जिम्मेदार ठहराया गया। Fe-HAp मैट्रिक्स में Zn इंफिल्ट्रेशन से क्षरण की दर में काफी वृद्धि हुई। इसका कारण गैल्वेनिक सेल का निर्माण बताया गया, जिसमें Fe-HAp ने कैथोड के रूप में कार्य किया और Zn ने एनोड के रूप में कार्य किया। Zn wt.% में वृद्धि के साथ, करोज़ोन पोटेन्शियल अधिक नकारात्मक पक्ष की ओर स्थानांतरित होता पाया गया और करोज़ोन करंट डेन्सिटी में वृद्धि पाई गई, जिससे संक्षारण प्रतिरोध में कमी का संकेत मिलता है। शुद्ध Fe सघन नमूने ने न्यूनतम वेट लॉस और संक्षारण दर को दर्शाया, जबकि Fe-3.5HAp-54Zn ने इमर्शन और इलेक्ट्रोकेमिकल परीक्षण में क्रमशः अधिकतम वेट लॉस और संक्षारण दर को दर्शाया। Fe-3.5HAp-54Zn के लिए अधिकतम वेट

लॉस और संक्षारण दर क्रमशः 6.98% और 2.38 mmpy पाई गई। सभी नमूनों में अच्छी साइटोकोम्पैटिबिलिटी पाई गई। Fe-HAp-Zn बायोमटेरियल ने अधिकतम सेल विऐबिलिटी दिखाई, जिसका श्रेय इस तथ्य को दिया गया कि Zn, Fe की तुलना में अधिक बायोकंपैटिबल है। सभी नमूनों में हेमोलिसिस अनुपात निर्धारित सीमा (5% से कम) के भीतर पाया गया। इसके अलावा, Fe-HAp-Zn ने न्यूनतम प्लेटलेट आसंजन दिखाया, जो उत्कृष्ट एंटीथ्रॉम्बोटिक गुण को दर्शाता है।

इमर्शन परीक्षण में वेट लॉस और इलेक्ट्रोकेमिकल परीक्षण में संक्षारण दर की भविष्यवाणी के लिए मॉडल प्राप्त करने के लिए बर्किंगम π थ्योरम का उपयोग करते हुए डिमेन्शनल एनालिसिस किया गया। प्रस्तावित मॉडलों द्वारा अनुमानित वैल्यू ने प्रयोगात्मक परिणामों के साथ एक मजबूत सहमति प्रदर्शित की। वेट लॉस और संक्षारण दर की भविष्यवाणी में अधिकतम त्रुटि क्रमशः 5.81% और 3.91% पाई गई। तुलनात्मक अध्ययन में TOFGC Fe-HAp-Zn बायोमटेरियल ने वर्तमान धातु बायोडिग्रेडेबल सामग्रियों की तुलना में बढ़ी हुई संक्षारण विशेषताओं के साथ-साथ उत्कृष्ट साइटोकोम्पैटिबिलिटी और हेमोकम्पैटिबिलिटी का प्रदर्शन किया। यह स्थापित किया गया कि विकसित Fe-HAp-Zn बायोमटेरियल में बेहतर संक्षारण दर, कम हेमोलिसिस अनुपात और उत्कृष्ट एंटीथ्रॉम्बोटिक संपत्ति के कारण आर्थोपेडिक अनुप्रयोगों के लिए बायोडिग्रेडेबल सामग्री होने की क्षमता है। इसके अलावा विकसित बायोमटेरियल के यांत्रिक और क्षरण गुणों को उपयुक्त अनुप्रयोग से मेल खाने के लिए तैयार किया जा सकता है।

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Abbreviations

3D	Three-Dimensional
2D	Two-Dimensional
Adj. MS	Adjusted mean square
ANOVA	Analysis of variance
BM	Biodegradable material
CA	Contact angle
CCD	Central composite design
CIP	Carbonyl iron particle
CPE	Constant phase element
CYS	Compressive yield strength
DF	Degree of freedom
DMEM	Dulbecco's Modified Eagle's Medium
DOE	Design of experiments
EDS	Energy dispersive spectroscopy
EIS	Electrochemical impedance spectroscopy
F	Fisher's value
GA	Genetic algorithm
HAp	Hydroxyapatite
HR	Heating rate
MWS	Microwave sintering
OCP	Open circuit potential
PBS	Phosphate buffer saline
PP	Potentiodynamic polarization
RDA	Recommended dietary allowance

SBF	Simulated body fluid
SCE	Saturated calomel electrode
SEM	Scanning electron microscopy
Seq. SS	Sequential sum of square
SLA	Stereolithography Apparatus
TOFGC	Topologically ordered functionally graded composite
UCS	Ultimate compressive strength
UTS	Ultimate tensile strength
XRD	X-ray diffraction

Nomenclature

α	Impedance parameter to the frequency
ρ	Density
ρ_{Fe-HAp}	Density of Fe-HAp
ρ_{Zn}	Density of zinc
σ_{cys}	Compressive yield strength
σ_{elec}	Conductivity of electrolyte (SBF)
C	Impedance parameter to the frequency
CPE_1	Capacitance of the external of the surface oxide film
CPE_2	Capacitance of the duplex layer due to corrosion products
CR	Corrosion rate
ρ_s	Sintered density
E_c	Compressive modulus of elasticity
E_{corr}	Corrosion potential
E_w	Equivalent weight
I_{corr}	Corrosion current
i_{corr}	Corrosion current density
$Im(Z)$	Imaginary part of impedance
OD	Optical density
R^2	Coefficient of determination
R_1	Resistance of the used electrolyte (SBF)
R_2	Solution resistance within pores of oxide film
R_3	Charged transfer resistance
$Re(Z)$	Real part of impedance

SA	Exposed surface area
T	Immersion time in SBF
t_{soak}	Soaking time
W_1	Warburg impedance
W_{Fe-HAp}	Weight in Fe-HAp in fabricated biomaterial
W_{loss}	Weight loss in immersion test
W_{Zn}	Weight in zinc in fabricated biomaterial
$wt\%$	Weight percentage